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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,470	01/07/2005	Thomas Tuschl	2923-673	5503

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
05/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/520,470	TUSCHL ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-20,22-36 and 38-41* is/are pending in the application.

4a) Of the above claim(s) *22-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-20,32-36 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 10, 2008 has been entered.

Status of Claims

Claims 1, 3-9, 11-16, 20, 22-36, and 38-41 are pending in the instant application as filed on March 10, 2008. Claims 22-31 have previously been withdrawn as being drawn to non-elected inventions. See applicant's reply filed on June 4, 2007. Accordingly, claims 1, 3-9, 11-16, 20, 32-36, and 38-41 are currently under examination on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9, 11-16, 20, 32-36, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tijsterman et al. (*Science,* January 2002, 295:694-697) in view of Elbashir et al. (*Nature* 2001, 411:494-498) and McSwiggen (US 2003/0153521 A1). The references are all citations of record.

The claims are drawn to a method of inhibiting a target transcript expression in human cells *in vitro,* comprising introducing a single-stranded RNA molecule that mediates RNA interference, wherein the molecule is 14-50 nucleotides in length, and at least 20 nucleotides at the 5' region are fully complementary to said target transcript, wherein the RNA molecule comprises at least one chemically modified sugar backbone or ribonucloetide, wherein the RNA molecule contains a pharmaceutically acceptable carrier that is a cationic liposome or covalently coupled to biodegradable polymers, the method is used for diagnostic applications.

Tijsterman et al. teach a method for inhibiting the transcript of target gene GFP comprising contacting a single-stranded RNA molecule that is 25 nucleotides in length (page 695). They also teach a method of triggering RNAi with unc-22 antisense single-stranded RNAs (page 695). They teach that *in vivo* siRNAs are predominantly expressed as antisense RNAs and

that first step of RNAi is bypassed by single-stranded antisense administration (pages 695-696). Furthermore, they teach that single-stranded antisense RNAs of at least 22 nucleotides and up to 40 nucleotides in length are capable of forming dsRNAs that become substrates for DICER-dependent degradation, therefore via RNAi (page 696). Tijsterman et al. do not teach that the method is performed in human cells *in vitro*, nor do they teach chemical modifications.

Elbashir et al. teach a method of inhibiting target transcript expression in mammalian cells *in vitro* by RNA interference, wherein the mammalian cells include cultured human cells. They teach that RNAi interference in human cell culture provides great analytical and investigational tools to study gene-specific therapeutics and gene function. See the entire reference.

McSwiggen teaches that RNAi-inducing RNA molecules can be chemically modified for increased stability. He also teaches that a 5'-phosphate moiety on the antisense strand of the RNAi-inducing RNA molecule is required for RNAi activity in cells and that the RNAi-inducing RNA molecule can be encapsulated in a liposome or covalently coupled to a biodegradable linker for delivery into cells (paragraphs 0112, 0139-0141, 0144-0145, 0154-0155, 0159, 0185, 0188, 0191-0192; claims 1-7, 19). He also teaches that RNAi-inducing RNA molecules such as siRNA molecules can be used as diagnostic tools (paragraphs 0233-0234).

It would have been obvious to one of ordinary skill in the art to modify the single-stranded RNAi molecule of Tijsterman et al. to include stabilizing chemical modifications of McSwiggen et al. and apply the chemically modified RNAi molecule to inhibit human genes in cultured human cells *in vitro* as taught by Elbashir et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the use of a single-stranded RNA molecule to inhibit target gene transcript expression by RNA interference was known in the art as taught by Tijsterman et al., and because incorporating chemical modifications such as the claimed 5'-phosphate moiety, phosphoramidate, and ethoxymethyl were known to increase stability of the RNAi-inducing molecules as taught by McSwiggen, and because RNA interference performed in cultured human cells was known to be useful for investigating gene-specific therapeutics or gene functional diagnostics as taught by Elbashir et al. Since both skills and knowledge necessary to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Applicant's arguments filed on March 10, 2008 have been fully considered but they are not persuasive. Applicant argues that Tijsterman et al. do not teach or suggest a method of inhibiting target gene expression in "mammalian" cells and that the *C. elegans* model used in Tijsterman et al's experiments does not render the claimed invention obvious because "evidence for RISC activity has not been found and thus the mechanism of action is believed to be different between *C. elegans* and mammals". In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., RISC activity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Note that the claims expressly recite that the target transcript expression is "inhibited by RNA-interference",

and Tijsterman et al. taught that target transcript expression was inhibited by RNA interference via a short antisense interfering RNA. Furthermore, it is an art-recognized, well-established scientific fact that RISC activity is a required element for RNA interference to occur, and therefore, the RNAi-mediated inhibition of target transcripts in Tijsterman et al. would have inherently involved the allegedly missing RISC activity. See for example Bernstein et al. (*Nature,* 2001, 409:363-366), who teach that RISC, a multicomponent nuclease, is the enzyme responsible for destroying target transcripts in a cell or any organism during the RNA interference process, whether the cell is of *Drosophila,* or *C. elegans,* or *Arabidopsis,* or mammals or yeast.

Applicant further argues that the antisense, single-stranded siRNA used in *C. elegans* of Tijsterman et al. does not suggest that "a single stranded RNA molecule can inhibit the expression of a target transcript *in vitro* in any and all organisms", because work in *C. elegans* is not predictive of results in mammals. Applicant is correct that the *C. elegans* is not representative of mammals, given the scientific fact that they have different physiology and thus belong to different animal phyla. However, in the instant case, the claimed methods are not directed to *in vivo* use of the single-stranded RNA molecule; they are merely drawn to *in vitro* methods of "inhibiting" target gene expression. Hence, whether or not the *C. elegans* animal model used in Tijsterman et al. is predictive or representative of the mammalian cells claimed in the instant case is not an issue, because the level of unpredictability of "inhibiting" a target transcript *in vitro* with a nucleic acid molecule was not high enough to necessitate undue experimentation for one of ordinary skill in the art to practice the entire scope of the *in vitro* methods, as it was routine in the art to inhibit a target transcript in mammalian cells *in vitro* with

a nucleic acid molecule at the time of the invention. For instance, see Elbashir et al. and McSwiggen, the other two cited prior art references in the instant case, who taught that one can inhibit target transcript expression in mammalian cells including human cells *in vitro* by RNA interference. Furthermore, the clamed use of a single-stranded RNA molecule that inhibits a target transcript by RNA interference was explicitly described in the teachings of Tijsterman et al. Hence, although the route of contacting the single-stranded siRNA molecule may be slightly different between the *C. elegans* of Tijsterman et al. (by injecting) and the claimed cultured mammalian cells (by transfecting or by "contacting" as claimed), the RNAi-mediated inhibition of target gene transcripts via a single-stranded siRNA molecule of Tijsterman et al. is identical to the inhibitory mechanism claimed in the instant case. Since the unpredictability level of inhibiting a target transcript in mammalian cells *in vitro* does not rise to the level of unreasonable or little or no expectation of success that would have required undue experimentation in view of the teachings of Tijsterman et al., Elbashir et al., and McSwiggen, one of ordinary skill in the art would have reasonably arrived at the claimed inhibition method.

In view of the foregoing, applicant's arguments for nonobviousness of the claimed invention are not sufficient to outweigh the obviousness set forth in this Office action as well as in the last two previous Office actions. Hence, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This is a continued examination under 37 CFR 1.114 of the instant application. All claims are drawn to the same invention claimed and examined in the prior Office action dated April 10, 2008. Further, claim 40, which was originally rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement in the Office action dated December 11, 2007, is within the scope of claim 20, which had been and remained rejected under 35 U.S.C. 103(a) in the last two Office actions. Since the claims being examined in the instant Office action are identical to those examined previously in the last Office action dated April 10, 2008, and substantially identical to those examined in the final Office action dated December 11, 2007, and therefore, same grounds of rejection and art of record from the last Office action are applied in this Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the request for a continuation examination has been filed. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 22-31 drawn to inventions nonelected without traverse in the reply filed on June 4, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635